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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,747	GRONTHOS ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79,81 and 84-90* is/are pending in the application.

4a) Of the above claim(s) *86-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79,81,84,85 and 90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/24/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 01/24/08 is acknowledged.

Claims 79, 81, 84-90 are pending.

Claims 86-89 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 79, 81, 84, 85 and 90 read on a method of generating a tissue, wherein a tissue is a mesenchymal tissue in a subject, comprising administering to a subject a population of STRO-1 ^{bright} cell are under consideration in the instant application.

In view of the amendment, filed 01/24/08 the following rejections remain

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 81 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection.**

" *a method of generating a tissue, wherein a tissue is a mesenchymal tissue selected from the group recited in claim 81* claimed in claims 81 represent(s) a departure from the specification and the claims as originally filed.

Applicant's arguments, filed 01/24/08 have been fully considered, but have not been found convincing.

Applicant asserts that disclosure of the instant Specification on pages 6, 7, 17, 18 clearly support the claimed spices of tissues that can be generated by administering STRO -1 ^{bright} cells.

Contrary to Applicant's assertions it is noted that the instant specification on page 18 only support a generic disclosure of "tissue in mammal". In re *Ruschig*. 154 USPQ 118----Where a species of a properly described genus was found not to be described. A generic or a sub-generic disclosure cannot support a species unless the species is specifically described. In addition, the Specification on pages 6 and 7 only disclosed that MPC are capable **of differentiation into at least two committed cell types**. There is no written support for the claimed " generation of mesenchymal tissue selected from the group recited in claim 81".

4. Claims 79, 81, 84, 85 and 90 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action, mailed on 10/19/07.

Applicant's arguments, filed 01/24/08 have been fully considered, but have not been found convincing.

Applicant asserts that the Specification on pages 41-43 provided an examples of mouse model in which expanded human cells were implanted subcutaneously. The bone lining cells, fibrous tissue and osteocytes within the newly formed bone were all identified as being positive for the alu sequence confirming their human origin. In addition the method stimulate generation of endogenous tissue such as fat and smooth muscle.

Contrary to Applicant's assertion, it is explicitly stated in the sited passage that " Fat and smooth surrounding the ceramic cubes **did not express the alu sequence** and was therefore presumed to have originated from the host (see page 41, line 34 in particular).

The specification only discloses detailed *in vitro* method for isolation and purification of SRTO-1 ^{bright} BM MPC (see examples 1 in particular). The Specification further disclosed *in vitro* studies of possible chondrogenic potential of said SRTO-1 ^{bright} BM MPC. However, the instant Specification explicitly stated that within SRTO-1 ^{bright} /VCAM-1 ^{brigh} BM fraction there are several additional sub-fractions that might have different developmental potential (see page 32 in particular). The specification does not adequately teach how to effectively generate any mesenchymal tissue in any subject, including humans by administering a population of STRO-1 ^{bright} cells. Moreover, no animals models were used to study the effectively of generating any mesenchymal tissue in any subject, including humans by administering a population of STRO-1 ^{bright} cells. Since there is no animal model studies and data in the specification to show the effectively of generating any mesenchymal tissue in any subject, including humans by administering a population of STRO-1 ^{bright} cells. it is unpredictable how

to correlate *in vitro* results with *in vivo* use . The specification does not teach how to extrapolate data obtained from *in vitro* studies to the development of effective *in vivo* mammalian therapeutic treatment, commensurate in scope with the claimed invention.

With regards to Applicant's comments that specification provided an examples of mouse model in which expanded human cells were implanted subcutaneously.

The fact that the bone lining cells, fibrous tissue and osteocytes within the newly formed bone were all identified as being positive for the alu sequence does not provided an enablement for the claimed method of generating any mesenchymal tissue in any subject, including human by administering STRO-1 ^{bright} cells . It is well know to one skill in the art that concerns were raised that the methods used to show that certain adult stem cells can jump lineage boundaries may be flawed, *e.g.*, if reliance had been placed solely on the appearance of Y chromosome-positive cells in a female recipient or even if markers such as β-galactosidase or GFP had been used. It has been suggested that the development of seemingly normal differentiated cells expressing a new marker might simply be due to the fusion of bone marrow cells with preexisting differentiated cells in the host's organs (Poulsom et al, 2003, J Am. Soc. Nephrol, V.14 pages s48-s54) . Holden et al. (Science, 2002, V.296, pages 2126-2129) teach that cells can mutate and develop markers characteristics of other lineages or that cells injected into a foreign tissue can take up local DNA and thus appears to have changes identity (see page 2126 in particular). Moreover, Holden et al. further teach that fusion scare has given further impetus to effort to establish rigorous standards for demonstrating plasticity such as: the cells must be properly identified at the outset, because a single alien cellin ostensibly purified culture could produce misleading results. The cells must contribute to the function of the host tissue. There is no evidence from the Specification that there was no fusion of said administered STRO-1 ^{bright} cells in recited examples. Moreover, Poulsom et al., further teach that extraordinary claims require extraordinary proof, and some have asked for a higher standard of evidence; requiring "a clonal approach" or demonstration of "a robust, sustained multi-lineage engraftment and functional activity representative of multiple phenotypic characteristics of the converted cells to show that full conversion has occurred" These criteria, put simply, are needed because showing partial repopulation of an organ with cells that have come to resemble their neighbors is not the same as showing a functional competence as diverse and broad as that expected of the indigenous population, yet this is what will be needed for tissue regeneration and for gene therapy strategies that rely on adult stem cell plasticity. We will need clonal expansion to yield all of the cell types normally produced, and only those, together with appropriate responses to the usual demands of growth, adaptation, and repair.

Hansson et al ., (Stem Cells, 2007, V.25, pages 1507-1510) teach that the data obtained on isolated stem cells *in vitro* has a limited , if any, correlation , for *in vivo* studies using said cells. The act of placing the stem cells into culture medium implies modifications which alters their biological properties compared to cells *in vivo*. Isolation and maintaining stem cells in vitro reqires a stringent selection for proliferation and adaptation to growth in tissue culture and thus **produces cells that have no counterpart in the normal animal** (emphases added). Thus, isolated stem cells *in vitro* can be viewed as something other than the stem cell existing as part of

a human body (see entire document, Abstract and page 1508 in particular). does not well correlate In addition, Cochlovius et al (Modern Drug Discovery, 2003, pages 33-38) teach that in contrast to in vitro models, and partly animal-human xenograft systems, tissue cells in vivo seems to express molecules for defense against cellular immune systems as well as against complement. Although these defense mechanisms are still poorly understood, they provide some hints as to why many potential therapeutics perform marvelously *in vitro* but a fairly high portion of them still fail *in vivo*. Thus, in the absence of working examples or detailed guidance in the specification, the intended uses of STRO-1 ^{bright} cells in the method of generating any mesenchymal tissue in any subject, including human are fraught with uncertainties.

Although, the specification describes several *in vitro* data, there is no correlation on this record between the said results and a claimed method of generating any mesenchymal tissue in any subject by administering STRO-1 ^{bright} cells in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to efficacy in humans or animals (emphasis added). Ex parte Maas, 9 USPQ2d 1746.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of generating any mesenchymal tissue in any subject by administering STRO-1 ^{bright} cells in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

The following new ground of objection is necessitated by the amendment filed 01/24/08

5. Claim 81 is objected to as being dependent on canceled claim 80.

Appropriate correction is required.

6. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571/ 272-0878.
The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Michail A Belyavskyi/
Primary Examiner, Art Unit 1644